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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PU0297-PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/SE2003/001784	International filing date (day/month/year) 17.11.2003	Priority date (day/month/year) 28.11.2002
International Patent Classification (IPC) or national classification and IPC C12N 15/10, B01D 15/08 // C07H 1/06, C07H 1/08		
Applicant Amersham Biosciences AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☒ (sent to the applicant and to the International Bureau) a total of 1 sheets, as follows:
 - ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

Date of submission of the demand 17.05.2004	Date of completion of this report 25.01.2005
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Micael Oswald /BS Telephone No. +46 8 782 25 00

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2003/001784

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

- ☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

- ☐ the international application as originally filed/furnished
- ☒ the description:
- pages 1-17 _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☒ the claims:
- pages _____ as originally filed/furnished
- pages* _____ as amended (together with any statement) under Article 19
- pages* 1 received by this Authority on 2004-10-19
- pages* _____ received by this Authority on _____
- ☒ the drawings:
- pages 1-5 _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2003/001784

Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-9</u>	YES
	Claims	_____	NO
Inventive step (IS)	Claims	<u>1-9</u>	YES
	Claims	_____	NO
Industrial applicability (IA)	Claims	<u>1-9</u>	YES
	Claims	_____	NO

2. Citations and explanations (Rule 70.7)

Documents cited in this International Report:

D1: Deshmukh RR, Warner TN, Hutchison F, Murphy M, Leitch WE 2nd, De Leon P, Srivatsa GS, Cole DL, Sanghvi YS. Large-scale purification of antisense oligonucleotides by high-performance membrane adsorber chromatography. *J Chromatogr A*. 2000 Aug 18;890(1):179-92.

D2: W00246398 A2.

D1 discloses high purity phosphorothionate antisense oligonucleotides.

D2, *inter alia*, discloses a chromatography column and an immobilized metal affinity chromatography (IMAC) resin.

The cited documents represent the general state of the art. The invention defined in claims 1-9 is not disclosed by any of these documents.

The cited prior art does not give any indication that would lead a person skilled in the art to the claimed invention. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1-9 is novel and is considered to involve an inventive step. The invention is industrially applicable.

AMENDED CLAIMS

1. A method of isolating fully thioated single stranded antisense oligonucleotides from a biological solution, which method comprises the steps of contacting the biological solution with an immobilised metal ion adsorption chromatography (IMAC) resin to adsorb antisense oligonucleotides to said resin and subsequently contacting the resin with an eluent under conditions that provide desorption of the antisense oligonucleotides from said resin, wherein the fully thioated antisense oligonucleotides are separated from incorrectly thioated antisense oligonucleotides in said solution.
2. A method according to claim 1, wherein the biological solution results from a synthesis of antisense oligonucleotides.
3. A method according to claim 1 or 2, wherein fully thioated antisense oligonucleotides are separated from incorrectly synthesised oligonucleotides.
4. A method according to any one of the preceding claims, wherein fully thioated antisense oligonucleotides are separated from incorrectly thioated antisense oligonucleotides containing 1-5, such as 1 or 2, bonds without thioation.
5. A method according to any one of the preceding claims, wherein the metal ion is Zr^{2+} or Fe^{3+} .
6. A method according to any one of the preceding claims, wherein the antisense oligonucleotides are of a size in the range of 5-30, and preferably 15-25, base pairs.
7. A method according to any one of the preceding claims, wherein the pH of the biological solution is below about 7 during the adsorption of antisense oligonucleotides.
8. A method according to any one of the preceding claims, which in addition comprises a subsequent step of polishing the isolated antisense oligonucleotides.
9. Use of an immobilised metal ion adsorption chromatography (IMAC) resin for isolation of fully thioated single stranded antisense oligonucleotides from incorrectly thioated antisense oligonucleotides in a biological solution.